Annex I

List of the names, pharmaceutical forms, strengths of the veterinary medicinal products, animal species, routes of administration, applicants / marketing authorisation holders in the Member States

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Austria	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Tribex 10% - orale Suspension für Rinder	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Austria	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver 50mg/ml Ijektionslösung für Rinder	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle
Austria	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver Combi 50 und 75 mg/ml Suspension zum Einggeben für Schafe und Lämmer	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep, lambs
Austria	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Injektionslösung für Schafe	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep
Austria	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Pour on solution for cattle	Closantel Ivermectin	*Information not available*	*Information not available*	*Information not available*	*Information not available*
Austria	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Injektionslösung für Rinder	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Austria	Novartis Animal Health GmbH Biochemiestr. 10 A-6250 Kundl AUSTRIA	Endex 19,5% - wässrige Suspension für Rinder	Triclabendazole Levamisole	120 mg/ml 75 mg/ml	Oral suspension	oral	Cattle
Austria	Pfizer Corporation Austria GmbH Floridsdorfer Hauptstrasse 1 A-1210 Wien AUSTRIA	Cydectin TriclaMox	Triclabendazole Moxidectin	50mg/ml 1mg/ml	Oral solution	oral	Sheep
Belgium	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Animec Super Solution for Injection for Cattle	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Belgium	Chanelle Pharmaceuticals Manufacturing Ltd. IDA Business & Technology Park Loughrea, Co. Galway IRELAND	Triclaben 10%	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Belgium	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Bimectin Plus 10/100 mg/ml	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Belgium	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver 5%	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle
Belgium	Merial Belgium S.A. Boulevard Sylvain Dupuis 243 B-1070 Bruxelles BELGIUM	Dovenix	Nitroxinil	250 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Belgium	Merial Belgium S.A. Boulevard Sylvain Dupuis 243 B-1070 Bruxelles BELGIUM	Ivomec F	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Belgium	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Solution for Injection for Cattle	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
Belgium	Novartis Consumer Health B.V. Claudius Prinsenlaan 142 4818 CP Breda THE NETHERLANDS	Endex 19,5	Triclabendazole Levamisole	12 g/100ml 7,5 g/100 ml	Oral suspension	oral	Cattle
Belgium	Virbac de Portugal Laboratórios LDA Rua Dionísio Saraiva, Lote 1, 1° Andar, Sala 2 2080-104 Almeirim PORTUGAL	Virbamec F	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Cyprus	Vetagrica Ltd 3 Othelou str. 2540 Dali Industrial Estate P.O.Box 17020 Nicosia CYPRUS	Ivomec Super injectable solution	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Czech Republic	Chanelle Pharmaceuticals Manufacturing Ltd. IDA Business & Technology Park Loughrea, Co. Galway IRELAND	Triclaben 100 mg/ml perorální suspenze pro skot	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Czech Republic	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	Ivomec Super solution for injection	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Czech Republic	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin solution for injection for cattle	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
Czech Republic	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin injekční roztok pro ovce	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep
Czech Republic	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin 5mg/ml+200 mg/ml Pour on solution for cattle	Closantel Ivermectin	200 mg/ml 5 mg/ml	Pour-on	pour-on use	Cattle
Denmark	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Bimectin Plus	Clorsulon Ivermectin	10 mg/ml 1 mg/ml	Solution for injection	subcutaneous	Cattle
Denmark	Pfizer Oy Animal Health Tietokuja 4 00330 Helsinki FINLAND	Cydectin TriclaMox	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Denmark	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Pour-On	Closantel Ivermectin	20 mg/ml 0.5 mg/ml	Pour-on	*Information not available*	Cattle
Denmark	Pfizer Oy Animal Health Tietokuja 4 00330 Helsinki FINLAND	Cydectin TriclaMox	Triclabendazol Moxidectin	200 mg/ml 5 mg/ml	Oral solution	*Information not available*	Cattle
Finland	Pfizer Oy Animal Health Tietokuja 4 00330 Helsinki FINLAND	Cydectin Triclamox	Triclabendazole Moxidectin	5 mg/ml 200 mg/ml	Pour-on	pour-on	Cattle
France	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Fascicur 5%	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
France	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Fascicur 10%	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
France	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Cevamec D	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
France	Janssen-Cilag 1 Rue Camille Desmoulins TSA 91003 92787 Issy Les Moulineaux Cedex 9 FRANCE	Flukiver	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep
France	Janssen-Cilag 1 Rue Camille Desmoulins TSA 91003 92787 Issy Les Moulineaux Cedex 9 FRANCE	Seponver	Closantel	50 mg/ml	Oral suspension	oral	Cattle, Sheep
France	Janssen-Cilag 1 Rue Camille Desmoulins TSA 91003 92787 Issy Les Moulineaux Cedex 9 FRANCE	Supaverm	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
France	Janssen-Cilag 1 Rue Camille Desmoulins TSA 91003 92787 Issy Les Moulineaux Cedex 9 FRANCE	Douvigard	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep
France	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	DOVENIX	Nitroxinil	250 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep
France	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	Ivomec D	Clorsulon Ivermectin	*Information not available*	Solution for injection	subcutaneous	*Information not available*

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
France	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Duotech	Closantel Oxfendazole	50 mg/ml 25 mg/ml	Oral suspension	oral	Sheep
France	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectine Solution Injectable Pour Cattles	Closantel Ivermectine	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
France	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectine Solution Injectable Pour Ovines	Closantel Ivermectine	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep
France	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Vermax D	Closantel Ivermectine	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
France	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Norofas Pour on	Closantel Ivermectine	200 mg/ml 5 mg/ml	Pour-on	pour-on	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Fascinex 5%	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep, Goat
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Fascinex 10%	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Fascinex Premelange	Triclabendazole	200 mg/ml	Premix	oral	Cattle
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Parsifal Bovins	Triclabendazole Levamisole	120 mg/ml 63,5 mg/ml	Oral suspension	oral	Cattle
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Parsifal Ovins	Triclabendazole Levamisole	50 mg/ml 32 mg/ml	Oral suspension	oral	Sheep
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Triclanil 5%	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Triclanil 10%	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Fascinex 100	Triclabendazole	100 mg/ml	Oral suspension	oral	Sheep
France	Novartis Santé Animale 14 Boulevard Richelieu 92500 Rueil Malmaison FRANCE	Fascinex 240	Triclabendazole	240 mg/ml	Oral suspension	oral	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
France	Pfizer Holding France 23/25 Avenue du Docteur Lannelongue 75014 Paris FRANCE	Cydectine Triclamox 1 mg/ml + 50 mg/ml Solution Buvable Pour Ovins	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep
France	Pfizer Holding France 23/25 Avenue du Docteur Lannelongue 75014 Paris FRANCE	Cydectine Triclamox 5 mg/ml + 200 mg/ml Solution pour Pour-on pour Bovins	Triclabendazole Moxidectin	200 mg/ml 5 mg/ml	Pour-on	pour-on	Cattle
France	Virbac de Portugal Laboratorios LDA Rua do Centro Empresarial Ed. 13, Quinta da Beloura 2710-693 Sintra PORTUGAL	Virbamec D Solution Injectable	Clorsulon Ivermectine	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Germany	AniMedica GmbH Im Südfeld 9 D-48308 Senden-Bösensell GERMANY	Endofluke 100 mg/ml orale Suspension	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle, sheep
Germany	AniMedica GmbH Im Südfeld 9 D-48308 Senden-Bösensell GERMANY	Endofluke	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Germany	Bimeda Chemicals Export a Division of Cross Vetpharm Group, Ltd. Broomhill Road TALLAGHT DUBLIN 24 IRELAND	Bimectin Fluke	Clorsulon Ivermectin	10 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Germany	Chanelle Pharmaceuticals Manufacturing Ltd. IDA Business & Technology Park Loughrea, Co. Galway IRELAND	Triclaben 10%	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Germany	Janssen-Cilag GmbH Johnson & Johnson Platz 1 D-41470 Neuss GERMANY	Flukiver	Closantel	50 mg/ml	Oral suspension	oral	Cattle, sheep
Germany	Janssen-Cilag GmbH Johnson & Johnson Platz 1 D-41470 Neuss GERMANY	Flukiver Combi	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral solution	oral	Sheep, lambs
Germany	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Pour-On	Closantel Ivermectin	200. mg/ml 5 mg/ml	Pour-on	pour-on	Cattle
Germany	Novartis Tiergesundheit GmbH Zielstattstr. 40 D-81379 München GERMANY	Fasinex 10%	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle, sheep
Germany	Pfizer GmbH Linkstr. 10 D-10785 Berlin GERMANY	Cydectin Triclamox 5 mg/ml	Triclabendazole Moxidectin	200 mg/ml 5 mg/ml	Pour-on	pour-on	Cattle
Germany	Pfizer GmbH Linkstr. 10 D-10785 Berlin GERMANY	Cydectin TriclaMox 1 mg/ml + 50 mg/ml Lösung zum Eingeben für Schafe	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Greece	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver Combi	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep, Lambs
Greece	New Vet 15 Fleming Street Maroussi 15123 GREECE	Zivet	Closantel Oxfendazole	5 mg/ml 2,5 mg/ml	Oral suspension	oral	Sheep
Greece	Pfizer Hellas AE Mesogeion 243 N.Psichiko 15451 GREECE	Cydectin Triclamox	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep
Greece	Provet Aspropyrgos 19300, Attik GREECE	Rafoxanide/Provet	Rafoxanide	300 mg/tab	Tablets	oral	Sheep
Hungary	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver 5 % injekció A.U.V.	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep
Hungary	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver Combi belsőleges szuszpenzió A.U.V.	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
Hungary	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	Ivomec Super injekció A.U.V.	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Iceland	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver Combi vet	Closantel	50/75 mg/ml	Oral solution	oral	Sheep, Lambs
Ireland	Biochem Ltd Pulleen Kanturk Co. Cork IRELAND	Levafluke	Rafoxanide Levamisole	22.5 mg/ml 15 mg/ml	Oral suspension	oral	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	C & H Generics Ltd c/o Michael McEvoy Seville House New Dock Street Galway IRELAND	Chanectin Super	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Chan Broad Spec	Rafoxanide Levamisole	22.5mg/ml 15 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Rafazole Oral Suspension	Rafoxanide Levamisole	30 mg/ml 30 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Ridafluke 3%	Rafoxanide	30 mg/ml	Oral suspension	oral	Cattle Sheep
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Animec Super	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Levatum Super	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Tribex 10% for cattle	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Tribex 5% for Sheep	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Triclaben 5% for Sheep	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
Ireland	Chanelle Pharmaceuticals Manufacturing Limited Dublin Road Loughrea Co. Galway IRELAND	Triclaben 10% for cattle	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Ireland	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Endofluke 10	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Fasifree 10%	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Bimectin Plus	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Ireland	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Mectaject Plus	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Ireland	Interchem Ireland Ltd Road M Unit 12 Tougher Business Park Newhall Naas Co. Kildare IRELAND	Orafluke 10%	Rafoxanide Fenbendazole	100 mg/ml 100 mg/ml	Oral suspension	oral	Cattle
Ireland	Interchem Ireland Ltd Road M Unit 12 Tougher Business Park Newhall Naas Co. Kildare IRELAND	Orafluke 5%	Rafoxanide Fenbendazole	50 mg/ml 50 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Intervet Ireland Ltd Magna Drive Magne Business Park Citywest Road Dublin 24 Ireland	Panafluke Oral Suspension	Rafoxanide Fenbendazole	45 mg/ml 30 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Flukiver 5 Injection	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Flukiver Combi Oral Suspension	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
Ireland	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Supaverm Oral Suspension	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
Ireland	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Flukiver Bovis	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle
Ireland	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Flukiver 5% w/v Oral Suspension	Closantel	50 mg/ml	Oral suspension	oral	Sheep
Ireland	Merial Animal Health Limited Sandringham House Sandringham Avenue, Harlow Business Park, Harlow CM19 5TG Essex UNITED KINGDOM	Ivomec super	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Ireland	Merial Animal Health Limited Sandringham House Sandringham Avenue, Harlow Business Park, Harlow CM19 5TG Essex UNITED KINGDOM	Trodax 34%	Nitroxinil	340 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Pour on	Closantel Ivermectin	200 mg/ml 5 mg/ml	Pour-on	pour-on	Cattle
Ireland	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
Ireland	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closiver for cattle	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
Ireland	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin for sheep	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep
Ireland	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closiver for sheep	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Combifluke Oral Suspension for Sheep	Closantel Oxfendazole	50 mg/ml 25 mg/ml	Oral suspension	oral	Sheep
Ireland	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Parafend Plus Oral Suspension for Sheep	Closantel Oxfendazole	50 mg/ml 25 mg/ml	Oral suspension	oral	Sheep
Ireland	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Duotech Oral Suspension for Sheep	Closantel Oxfendazole	50 mg/ml 25 mg/ml	Oral suspension	oral	Sheep
Ireland	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Endex 19.5%	Triclabendazole Levamisole	120 mg/ml 75 mg/ml	Oral suspension	oral	Cattle
Ireland	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Endex 8.75%	Triclabendazole Levamisole	50 mg/ml 35 mg/ml	Oral suspension	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex 10%	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Ireland	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex 10% for Sheep	Triclabendazole	100 mg/ml	Oral suspension	oral	Sheep
Ireland	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex 5%	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
Ireland	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex 24%	Triclabendazole	240 mg/ml	Oral suspension	oral	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex Super 19.5%	Triclabendazole Levamisole	120 mg/ml 75 mg/ml	Oral suspension	oral	Cattle
Ireland	Pfizer Healthcare Ireland 9 Riverwalk National Digit Park Citywest Business Campus Dublin 24 IRELAND	Cydectin Triclamox	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral suolution	oral	Sheep
Ireland	PharVet Ltd Station Road Bagenalstown Co. Carlow IRELAND	Fenafluke 5%	Rafoxanide Fenbendazole	50 mg/ml 50 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	PharVet Ltd Station Road Bagenalstown Co. Carlow IRELAND	Triazole	Rafoxanide Levamisole	22.5 mg/ml 15 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Quinn's Chemist Bridge Street Crossmolina Co. Mayo IRELAND	Fluken worm	Rafoxanide Levamisole	22.5 mg/ml 15 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Univet Limited Tullyvin Cootehill Co. Cavan IRELAND	Curafluke 10%	Rafoxanide Fenbendazole	100 mg/ml 100 mg/ml	Oral suspension	oral	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	Univet Limited Tullyvin Cootehill Co. Cavan IRELAND	Curafluke 5%	Rafoxanide Fenbendazole	50 mg/ml 50 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Univet Limited Tullyvin Cootehill Co. Cavan IRELAND	Flukex 9%	Rafoxanide	90 mg/ml	Oral suspension	oral	Cattle
Ireland	Univet Limited Tullyvin Cootehill Co. Cavan IRELAND	Univet Multidose Fluke and Worm	Rafoxanide Levamisole	22.5 mg/ml 15 mg/ml	Oral suspension	oral	Cattle, Sheep
Ireland	Virbac S.A. Virbac 1, 1ère Avenue 2065 M - L.I.D., BP 27, 06516 Carros, Cedex FRANCE	Virbamec super	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Italy	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Maximec Plus	Clorsulon Ivermectin	*Information not available*	Solution for injection	*Information not available*	Cattle
Italy	FATRO S.p.A. Via Emilia 285 40064 Ozzano Emilia (BO) ITALY	Tolomec Plus	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Italy	Pfizer Italia s.r.l. Via Isonzo 71 LATINA ITALY	Cydectin Triclamox	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Italy	Intervet Production s.r.l. via Nettunense km 20,300 Aprilia (LT) ITALY	Ranigel	Rafoxanide	75 mg/ml	Solution for injection	subcutaneous	Cattle
Italy	Intervet Production s.r.l. via Nettunense km 20300 Aprilia (LT) ITALY	Ranigel	Rafoxanide	30 mg/ml	Oral suspension	oral	Cattle, Sheep
Italy	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver	Closantel	50 mg/ml	Solution for injection	intramuscular	Cattle
Italy	Janssen-Cilag S.p.A. Via M. Buonarroti 23 20093 Cologno Monzese (MI) ITALY	Seponver	Closantel	50 mg/ml	Oral suspension	oral	Sheep
Italy	Janssen-Cilag S.p.A. Via M. Buonarroti 23 20093 Cologno Monzese (MI) ITALY	Seponver Plus	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
Italy	Merial Italia S.p.A. via Vittorio Pisani, 16 20100 Milano ITALY	Ivomec Plus	Clorsulon Ivermectin	100 mg/ml 1 mg/ml	Solution for injection	subcutaneous	Cattle
Italy	Norbrook Laboratories Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Duotech	Closantel Oxfendazole	50 mg/ml 25 mg/ml	Oral suspension	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Italy	Norbrook Laboratories Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep
Italy	Norbrook Laboratories Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Pour on	Closantel Ivermectin	*Information not available*	*Information not available*	*Information not available*	*Information not available*
Italy	Pfizer Italia s.r.l. Via Isonzo 71 LATINA ITALY	Cydectin Triclamox Pour on	Triclabendazole Moxidectin	*Information not available*	Pour-on	pour-on	Cattle
Italy	Virbac de Portugal Laboratorios LDA Rua do Centro Empresarial Ed. 13, Quinta da Beloura 2710-693 Sintra PORTUGAL	Virbamec F	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Latvia	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	Ivomec Super solution for injection	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Lithuania	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	Ivomec Super solution for injection	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Luxembourg	Merial Belgium S.A. Boulevard Sylvain Dupuis 243 B-1070 Bruxelles BELGIUM	Ivomec F	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Luxembourg	Pfizer Animal Health S.A. rue Laid Burniat 1 1348 Luvain-la-Neuve BELGIUM	Cydectin Triclamox	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep
Norway	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Duotech vet	Closantel Oxfendazole	50 mg/ml 25 mg/ml	oral suspension	oral	Sheep
Portugal	Esteve Farma LDA Av. Do Forte, 3 Edifício Suécia III, Piso 1 2794-044 Carnaxide PORTUGAL	Flukiver 50 mg/ml solução injectável para bovinos e ovinos	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep
Portugal	Esteve Farma LDA Av. Do Forte, 3 Edifício Suécia III, Piso 1 2794-044 Carnaxide PORTUGAL	SEPONVER PLUS (75 mg + 50 mg) suspensão oral para ovinos	Closantel Mebendazol	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
Portugal	Esteve Farma LDA Av. Do Forte, 3 Edifício Suécia III, Piso 1 2794-044 Carnaxide PORTUGAL	Flukiver 5% suspensão oral	Closantel	50 mg/ml	Oral suspension	oral	Cattle, Sheep
Portugal	Merial Portuguesa Saúde Animal, Lda Av. Maria Lamas, Lt.19 - BL A - Piso 2 - Serra das Minas 2635-432 Rio de Mouro PORTUGAL	DOVENIX	Nitroxinil	250 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Portugal	Merial Portuguesa Saúde Animal, Lda Av. Maria Lamas, Lt.19 - BL A - Piso 2 - Serra das Minas 2635-432 Rio de Mouro PORTUGAL	IVOMEC F	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Portugal	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Duotech Suspensão	Closantel Oxfendazole	50 mg/ml 25 mg/ml	Oral suspension	oral	Sheep
Portugal	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin FF, solução injectável para bovinos	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
Portugal	Virbac de Portugal Laboratórios LDA Rua Dionísio Saraiva, Lote 1, 1° Andar, Sala 2 2080-104 Almeirim PORTUGAL	Virbamec F	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Romania	Bomac Laboratories Limited Cnr Wiri Station Road & Hobill Ave P.O Box 76-369 Manukau City Auckland NEW ZEALAND	Clos-Atak	Closantel	50 mg/ml	Solution for injection	Intramuscular / subcutaneous	Cattle, Sheep
Romania	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer THE NETHERLANDS	Ranigel	Rafoxanide	30 mg/ml	Oral suspension	oral	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Romania	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer THE NETHERLANDS	Fluxacur	Triclabendazole Abamectin	*Information not available*	Oral suspension	oral	Cattle Sheep
Romania	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver 5%	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle
Romania	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver Combi	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
Romania	Kepro B.V. Maagdenburgstraat 38 7421 ZE Deventer THE NETHERLANDS	Kepromec Super	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Romania	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	IVOMEC PLUS	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Romania	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	DOVENIX	Nitroxinil	25 g/100ml	Solution for injection	injectable solution	Cattle, Sheep, Goats
Romania	Pasteur - Filiala Filipesti SRL Str. Principala nr. 944 Filipestii de Padure Jud. Prahova ROMANIA	Evomec Plus	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Romania	Pasteur - Filiala Filipesti SRL Str. Principala nr. 944 Filipestii de Padure Jud. Prahova ROMANIA	Helmizol Plus	Clorsulon	120 mg/bolus	Bolus	oral	Cattle
Romania	S.C. Romvac Company s.a. Şos. Centurii, nr. 7 Voluntari ROMANIA	Fasciocid	Triclabendazole	100 mg/ml	Oral solution	oral	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Romania	S.C. Romvac Company s.a. Şos. Centurii, nr. 7 Voluntari ROMANIA	Romavermectina B1 1% Plus	Clorsulon Ivermectin	100 mg/ml 10mg/ml	Solution for injection	subcutaneous	Cattle
Romania	Vanelli S.R.L. Iaşi-Tg. Frumos, km. 10 Iaşi ROMANIA	Ascacid Forte	Rafoxanide Albendazole	25 mg/ml 28 mgml	Oral suspension	oral	Cattle, Sheep
Romania	VIM Spectrum S.R.L. Sos. Sighisoarei nr.409 Tg. Mures ROMANIA	Distol	Triclabendazole Ivermectin	500 mg/tablet 10 mg/tablet	Tablets	oral	Sheep, Goats
Slovak Republic	Chanelle Pharmaceuticals Manufacturing Ltd. IDA Business & Technology Park Loughrea, Co. Galway IRELAND	Triclaben 100 mg/ ml por.sus.ad us.vet.	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Slovak Republic	Merial S.A.S. 29 Avenue Tony Garnier 69007 Lyon FRANCE	Ivomec Super inj. ad us.vet.	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Slovak Republic	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin inj. ad us.vet.	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
Slovak Republic	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin injekčný roztok pre ovce	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Slovak Republic	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin 5mg/ml+200 mg/ml Pour on solution for Cattle	Closantelum Ivermectinum	200 mg/ml 5 mg/ml	Pour on	pour-on	Cattle
Slovenia	KRKA tovarna zdravil, d.d. Šmarješka cesta 6 8501 Novo Mesto SLOVENIA	Fascoverm	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep
Slovenia	KRKA tovarna zdravil, d.d. Šmarješka cesta 6 8501 Novo Mesto SLOVENIA	FASCOVERM PLUS	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
Spain	C & H Generics Limited c/o Michael McEvoy & Co Seville House New Dock Street Galway IRELAND	Chanectin	Ivermectin Clorsulon	*Information not available*	*Information not available*	*Information not available*	Cattle
Spain	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Tribex 10% Suspension Oral Para Bovino	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Spain	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Animec Plus Solución inyectable para bovino	Clorsulon Ivermectin	*Information not available*	*Information not available*	*Information not available*	*Information not available*
Spain	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Tribex 5% Solución Oral Para Ovino	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain	Chanelle Pharmaceuticals Manufacturing Ltd. IDA Business & Technology Park Loughrea, Co. Galway IRELAND	Alverin Plus solution for injection for cattle	Clorsulon Ivermectin	*Information not available*	*Information not available*	*Information not available*	*Information not available*
Spain	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Bimectin Plus	Clorsulon Ivermectin	*Information not available*	*Information not available*	*Information not available*	*Information not available*
Spain	Diana S.A.E. Ctra Barcelona-Ripoll, PK 17 08150 Parets Del Valles, Barcelona SPAIN	Vermifor Ecto	Closantel	5 g/100 ml	Solution for injection	intramuscular / subcutaneous /	Cattle, Sheep
Spain	FATRO Iberica, S.L. C/ Constitución 1, Planta Baja 3 08960 Sant Just Desvern Barcelona SPAIN	Fugosantel	Closantel	5 g/100 ml	Solution for injection	intramuscular / subcutaneous	Cattle, Sheep
Spain	Industrial Veterinaria, S.A. Esmeralda, 19 E-08950 Esplugues de Llobregat (Barselona) SPAIN	Rolenol	Closantel	50 mg/ml	Solution for injection	intramuscular / subcutaneous	Cattle, Sheep
Spain	Laboratorios Cenavisa, s.a. Cami Pedro Estela, S/N 43205 Reus (Tarragona) SPAIN	Telcen	Closantel	50 mg/ml	Solution for injection	intramuscular / subcutaneous	Cattle, Sheep
Spain	Laboratorios Dr. Esteve S.A. Avda. Mare de Déu de Montserrat 221 08041 Barcelona SPAIN	Flukiver	Closantel	5 g/100 ml	Solution for injection	subcutaneous	Cattle, Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain	Laboratorios Dr. Esteve S.A. Avda. Mare de Déu de Montserrat 221 08041 Barcelona SPAIN	Seponver Plus	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep
Spain	Laboratorios e Industrias IVEN S.A. C/ Luis I 56 Pol. Ind. De Vallecas Madrid SPAIN	Endoectiven	Closantel	50 mg/ml	Solution for injection	intramuscular / subcutaneous	Cattle, Sheep
Spain	Laboratorios Hipra S.A. Avda. La Selva 135 17170 Amer (Gerona) SPAIN	Leclosan	Closantel	50 mg/ml	Solution for injection	intramuscular / subcutaneous	Cattle, Sheep
Spain	Laboratorios Ovejero, S.A. Ctra León - Vilecha, 30 24192 León SPAIN	Distomicide	Nitroxinil	25 g/100ml	Solution for injection	subcutaneous	Cattle, Sheep
Spain	Merial Laboratorios S.A. C/ Tarragona n.161 Locales D/E 08014 Barcelona SPAIN	Dovenix	Nitroxinil	25 g/100ml	Solution for injection	subcutaneous	Cattle, Sheep
Spain	Merial Laboratorios S.A. C/ Tarragona n.161 Locales D/E 08014 Barcelona SPAIN	Ivomec F	Clorsulon	100 mg/ml	Solution for injection	subcutaneous	Cattle
Spain	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin pour-on	Closantel Invermectine	*Information not available*	*Information not available*	pour-on	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Duotech suspensión oral	Closantel Oxfendazol	50 mg/ml 25 mg/ml	Oral suspension	oral	Sheep
Spain	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Solucion Inyectable para Bovino	Closantel Invermectine	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
Spain	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Solucion Inyectable para Ovino	Closantel Invermectine	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep
Spain	Novartis Sanidad Animal S.L. C/ De La Marina 206 08013 Barcelona SPAIN	Endex 19,5%	Triclabendazole	12 g/100 ml	Oral suspension	oral	Cattle
Spain	Novartis Sanidad Animal S.L. C/ De La Marina 206 08013 Barcelona SPAIN	Fasinex 10% Bovino	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
Spain	Novartis Sanidad Animal S.L. C/ De La Marina 206 08013 Barcelona SPAIN	Fasinex 5% Ovino	Triclabendazole	5 g/100 ml	Oral suspension	oral	Sheep
Spain	Novartis Sanidad Animal S.L. C/ De La Marina 206 08013 Barcelona SPAIN	Endex 8,57%	Triclabendazole Levamisole	5 g/100 ml 3,75 g/100 ml	Oral suspension	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain	Novartis Sanidad Animal S.L. C/ De La Marina 206 08013 Barcelona SPAIN	Fasinex 10% Ovino	Triclabendazole	100 mg/ml	Oral suspension	oral	Sheep
Spain	Pfizer S.L. Avenida de Europa 20 B Parque Empresarial La Moraleja Alcobendas Madrid SPAIN	Cydectin Triclamox 5 Mg/Ml + 200 Mg/Ml Pour On Solution For Cattle	Triclabendazole Moxidectin	*Information not available*	*Information not available*	*Information not available*	*Information not available*
Spain	Pfizer S.L. Avenida de Europa 20 B Parque Empresarial La Moraleja Alcobendas Madrid SPAIN	Cydectin Triclamox 1 mg/ml + 50 mg/ml Solución Oral Para Ovino	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep
Spain	S.P. Veterinaria S.A. Ctra Reus a Vinyols Km.4,1 43330 Riudoms (Tarragona) SPAIN	Endoex Inyectable	Closantel	5 g/100ml	Solution for injection	intramuscular / subcutaneous	Cattle, Sheep
Spain	S.P. Veterinaria S.A. Ctra Reus a Vinyols Km.4,1 43330 Riudoms (Tarragona) SPAIN	Endoex Oral	Closantel	5 g/100 ml	Oral solution	oral	Cattle, Sheep
Spain	Virbac de Portugal Laboratórios LDA Rua Dionísio Saraiva, Lote 1, 1° Andar, Sala 2 2080-104 Almeirim PORTUGAL	Virbamec F	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
Sweden	Pfizer Oy Animal Health Tietokuja 4 00330 Helsinki FINLAND	Moxidektin/ Triklabendazol Fort Dodge	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
The Netherlands	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Tribex 5% orale suspensie voor schapen	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
The Netherlands	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Tribex 10% orale suspensie voor rundvee	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
The Netherlands	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver 50 mg/ml, oplossing voor injectie	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle
The Netherlands	Janssen Pharmaceutica N.V. 30 Turnhoutseweg B-2340 Beerse BELGIUM	Flukiver combi orale suspensie voor schapen en lammeren	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep, Lambs
The Netherlands	Merial B.V. Kleermakersstraat 10 1191 JL Velserbroek THE NETHERLANDS	Ivomec Plus	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	oral	Cattle
The Netherlands	Novartis Consumer Health B.V. Claudius Prinsenlaan 142 4818 CP Breda THE NETHERLANDS	Endex 19.5 %	Triclabendazole Levamisole	120 mg/ml 75 mg/ml	Oral suspension	oral	Cattle
The Netherlands	Novartis Consumer Health B.V. Claudius Prinsenlaan 142 4818 CP Breda THE NETHERLANDS	Endex 8.75%	Triclabendazole Levamisole	50 mg/ml 37,5 mg/ml	Oral suspension	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
The Netherlands	Novartis Consumer Health B.V. Claudius Prinsenlaan 142 4818 CP Breda THE NETHERLANDS	Fasinex 10%	Triclabendazole	10 g/100ml	Oral suspension	oral	Cattle
The Netherlands	Novartis Consumer Health B.V. Claudius Prinsenlaan 142 4818 CP Breda THE NETHERLANDS	Fasinex 5%	Triclabendazole	5 g/100ml	Oral suspension	oral	Sheep
The Netherlands	Pfizer Animal Health B.V. Rivium Westlaan 142 2909 LD Capelle a/d Ijssel THE NETHERLANDS	Cydectin Triclamox 1 mg/ml + 50 mg/ml orale oplossing voor schapen	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep
The Netherlands	Schippers Europe B.V. Rond Deel 12 5531 AH Bladel THE NETHERLANDS	Endex	Triclabendazole Levamisole	50 mg/ml 37,5 mg/ml	Oral suspension	oral	Sheep
The Netherlands	Virbac de Portugal Laboratorios LDA Rua do Centro Empresarial Ed. 13, Quinta da Beloura 2710-693 Sintra PORTUGAL	Virbamec F. oplossing voor injectie	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
The Netherlands	Wirtz Farma B.V. Leijsendwarsstraat 26 4901 PG, Oosterhout THE NETHERLANDS	Endex Suspensie	Triclabendazole Levamisole	50 mg/ml 37,5 mg/ml	Oral suspension	oral	Sheep
The Netherlands	Wirtz Farma B.V. Leijsendwarsstraat 26 4901 PG, Oosterhout THE NETHERLANDS	Fasinex 5%	Triclabendazole	5 g/100ml	Oral suspension	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
The Netherlands	Wirtz Farma B.V. Leijsendwarsstraat 26 4901 PG, Oosterhout THE NETHERLANDS	Fasinex 10%	Triclabendazole	10 g/100ml	Oral suspension	oral	Cattle
United Kingdom	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Alverin Plus Solution for Injection for Cattle	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Animec Super Solution for Injection for Cattle	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Tribex 5% Oral Suspension for Sheep	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
United Kingdom	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Tribex 10% Oral Suspension for Cattle	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
United Kingdom	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Triclacert 5% Oral Suspension for Sheep	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
United Kingdom	Chanelle Animal Health Limited 7 Rodney Street Liverpoool L1 9HZ UNITED KINGDOM	Triclacert 10% Oral Suspension for Cattle	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
United Kingdom	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Bimectin Plus Solution for Injection for Cattle	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Cross Vet Pharm Group Ltd Broomhill Road Tallaght Dublin 24 IRELAND	Endofluke 100 mg/ml Oral Suspension	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle, Sheep
United Kingdom	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Flukiver 5% w/v Oral Suspension	Closantel	50 mg/ml	Oral suspension	oral	Sheep
United Kingdom	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Flukiver Bovis 50 mg/ml Solution for Injection	Closantel	50 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Mebadown Super Oral Suspension	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep, Lambs
United Kingdom	Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Buckinghamshire HP12 4EG UNITED KINGDOM	Supaverm Oral Suspension	Closantel Mebendazole	50 mg/ml 75 mg/ml	Oral suspension	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
United Kingdom	Merial Animal Health Limited Sandringham House Sandringham Avenue, Harlow Business Park, Harlow CM19 5TG Essex UNITED KINGDOM	Ivomec Super Injection for Cattle	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Merial Animal Health Limited Sandringham House Sandringham Avenue, Harlow Business Park, Harlow CM19 5TG Essex UNITED KINGDOM	Trodax 34% w/v Solution for Injection	Nitroxinil	340 mg/ml	Solution for injection	subcutaneous	Cattle, Sheep
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Pour-on Solution for Cattle	Closantel Ivermectin	200 mg/ml 5 mg/ml	Pour-on	pour-on	Cattle
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Solution for Injection	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closamectin Solution for Injection for Sheep	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closiver Pour-on Solution for Cattle	Closantel Ivermectin	200 mg/ml 5 mg/ml	Pour-on	pour-on	Cattle
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closiver Solution for Injection for Cattle	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closiver Solution for Injection for Sheep	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Sheep
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Closivet Solution for Injection for Cattle	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Norofas Pour-On	Closantel Ivermectin	200 mg/ml 5 mg/ml	Pour-on	pour-on	Cattle

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Norofas Solution for Injection	Closantel Ivermectin	125 mg/ml 5 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Norbrook Laboratories Ltd Station Works Camlough Road Newry, County Down BT35 6JP Northern Ireland UNITED KINGDOM	Triclafas Drench 5% w/v Oral Suspension	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
United Kingdom	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Combinex Cattle Oral Suspension	Triclabendazole Levamisole	120 mg/ml 75 mg/ml	Oral suspension	oral	Cattle
United Kingdom	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Combinex Oral Suspension	Triclabendazole Levamisole	50 mg/ml 37,5 mg/ml	Oral suspension	oral	Sheep
United Kingdom	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasimec Duo S 0.1%/5% Oral Suspension for Sheep	Triclabendazole Ivermectin	50 mg/ml 1 mg/ml	Oral suspension	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
United Kingdom	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex 5% w/v Oral Suspension	Triclabendazole	50 mg/ml	Oral suspension	oral	Sheep
United Kingdom	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex 10% Oral Suspension for Cattle	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle
United Kingdom	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex 100 10%(w/v) Oral Suspension for Cattle and Sheep	Triclabendazole	100 mg/ml	Oral suspension	oral	Cattle, Sheep
United Kingdom	Novartis Animal Health United Kingdom Limited Frimley Business Park Frimley Camberley Surrey GU16 7SR UNITED KINGDOM	Fasinex 240, 24% w/v Oral Suspension for Cattle	Triclabendazole	240 mg/ml	Oral suspension	oral	Cattle
United Kingdom	Pfizer Ltd Ramsgate Road Sandwich Kent CT13 9NJ UNITED KINGDOM	Cydectin TriclaMox 1 mg/ml + 50 mg/ml Oral Solution for Sheep	Triclabendazole Moxidectin	50 mg/ml 1 mg/ml	Oral solution	oral	Sheep

Member State EU/EEA	Applicant/ Marketing Authorisation Holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
United Kingdom	Pfizer Ltd Ramsgate Road Sandwich Kent CT13 9NJ UNITED KINGDOM	Cydectin TriclaMox 5 mg/ml + 200 mg/ml Pour-on Solution for Cattle	Triclabendazole Moxidectin	200 mg/ml 5 mg/ml	Pour-on	*Information not available*	Cattle
United Kingdom	Virbac de Portugal Laboratórios LDA Rua Dionísio Saraiva, Lote 1, 1° Andar, Sala 2 2080-104 Almeirim PORTUGAL	Supremadex Solution for Injection	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle
United Kingdom	Virbac Ltd Woolpit Business Park Windmill Avenue Woolpit Bury St Edmunds Suffolk IP30 9UP UNITED KINGDOM	Virbamec Super Solution for Injection	Clorsulon Ivermectin	100 mg/ml 10 mg/ml	Solution for injection	subcutaneous	Cattle

Annex II

Scientific conclusions and grounds for amendment of the summaries of product characteristics and package leaflets

Overall summary of the scientific evaluation of veterinary medicinal products containing active substances belonging to the class of flukicides for which no maximum residue limit has been established in milk and which are intended for use in ruminants producing milk for human consumption (*see Annex I*)

1. Introduction

Flukicidal substances are anthelmintics which are active against parasites belonging to the class of trematodes. *Fasciola hepatica* (common name: liver fluke), is the causative agent of fasciolosis, one of the most economically important helminth diseases of livestock worldwide. Both the immature and mature flukes are harmful to the target species, and each flukicide has varying efficacy against different ages of fluke.

The control of liver fluke is achieved primarily by treatment with veterinary medicinal products containing flukicidal substances and is also assisted by appropriate husbandry measures (e.g. not grazing low-lying pastures or wet pastures near ponds and streams).

On 14 February 2011, the European Commission initiated a referral under Article 35 of Directive 2001/82/EC, as amended, for all veterinary medicinal products containing active substances belonging to the class of flukicides for which no MRL has been established in milk intended for use in all ruminants producing milk for human consumption. Due to the absence of a MRL in milk these products are not authorised for use in lactating animals. They have been used during the dry period with different precautionary measures including safety spans prior to calving,or lambing/kidding. The CVMP was therefore requested to give its opinion as to whether measures are necessary to ensure that the use, during the non-lactating period, of veterinary medicinal products containing flukicidal substances for which a MRL has not been established in milk, would not lead to residues in milk that, combined with residues of these flukicidal substances from other foodstuffs, would result in consumer exposure exceeding the ADI. The Committee was also asked to recommend whether the marketing authorisations should be maintained, varied, suspended or withdrawn.

2. Discussion

The flukicidal substances for which a MRL has not been established in milk and that are included as active substances in authorised veterinary medicinal products in the Member States (EU/EEA) are clorsulon, closantel, nitroxinil, rafoxanide and triclabendazole. The CVMP collected information from national competent authorities on veterinary medicinal products containing these substances. This led to the identification of 251 products. From these 251 veterinary medicinal products, 96 contain one of the substances mentioned above as a single active substance and the remaining 155 are combination products containing a second non-flukicidal active substance. In order to establish the overall appropriateness of the product information with regard to the use in dairy animals the second active substance would need to be considered. As the scope of the referral was restricted to flukicidal substances only, the second active substance in the combination products was not evaluated.

Approach taken by CVMP

To determine whether residues in milk would result in overall exposure to residues over the ADI it is necessary to know what portion of the ADI is available to accommodate residues in milk (i.e., what

portion of the ADI is not already accounted for by exposure to residues present in other food commodities), and the concentration of residues in milk at relevant time points.

Where adequate residue data in milk are available these are used to calculate the time required between drug administration and calving or lambing/kidding to ensure that residues in milk do not result in consumer total exposure to residues over the ADI.

However, it was noted that, in many cases, adequate residue depletion data in milk from dairy animals treated during the non-lactating period is not available. The Committee agreed that, in such cases, and where possible, milk concentrations could be estimated by extrapolation from plasma concentrations. This can be done by using empirically derived milk to plasma ratios or, in principle, by using appropriate pharmacokinetic data (as described by Rasmussen, 1966[1]). The Committee emphasised that while such an approach may provide a useful tool for estimating residue levels in milk in the absence of milk data, the approach would not be acceptable for the establishment of MRL values.

Residue data in milk and plasma are evaluated using the approaches described in the CVMP Note for guidance for the determination of withdrawal periods for milk (EMEA/CVMP/473/98-FINAL), using the time to safe concentration (TTSC) approach where possible (i.e. where residues in all animals fall below the level considered safe within the time span for which data are available), and using the safe concentration for linear regression (SCLR) approach where the TTSC method is not appropriate (i.e. where it is necessary to extrapolate from the available data in order to determine the time point at which residues fall below the level considered safe). It is acknowledged that the guidance relates to methods for establishing withdrawal periods for milk, however, because the type of data to be evaluated in this referral is similar to that typically evaluated for the establishment of withdrawal periods, the use of these approaches is considered appropriate here. In those cases where appropriate information on residue levels in milk or plasma are not available, a more stringent pharmacokinetic approach can be employed to calculate the time needed to allow elimination of a sufficient amount of residues to ensure that the quantity of residues remaining in the animal's body is such that if all remaining residues were present in 1.5 l milk[2], the consumer's overall exposure to residues (including residues present in other food commodities) would not be above the ADI. In the remainder of this opinion this is referred to as 'the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk'. While this approach was acknowledged to be conservative, in the absence of alternative relevant data, it does provide a means for estimating a time point at which residues in milk can be concluded to be safe.

The evaluation detailed in this opinion attempts to address the issue raised by the European Commission on the basis of the available data. However, it must be emphasised that these data are limited, with very few studies specifically addressing the depletion of residues of relevant substances in dry cattle/sheep/goats. The amount and quality of available data are not comparable with that which would normally form the basis for the establishment of MRLs or withdrawal periods and as a result, the recommendations made are general and conservative, and are not product specific - no distinction is made to account for formulation or strength differences, or for dosage differences. It is assumed that the recommendations are sufficiently conservative to overcome any concerns relating to these issues. While the general nature of the recommendations has its limitations, the approach used aims to provide pragmatic use of limited resources.

[1] Rasmussen, F. (1966) Studies on the mammary excretion and absorption of drugs. Thesis. Carl Fr. Mortensen, Copenhagen 1966.
[2] Estimated daily consumption according to standard food basket for the calculation of the theoretical maximum daily intake of residues and calculation of maximum residue limits

Predicting residue levels in milk based on data in plasma

In the majority of cases transfer of substances from blood plasma to milk (and *vice versa*) is governed by simple diffusion across the mammary gland epithelium (Rasmussen, 1966); active transport has been rarely reported (Ito and Lee, 2003)[3]. This implies that in general, the ratio between the concentration of a drug in plasma and the concentration in milk will remain constant over time. The milk to plasma ratio for a substance can be established based on empirical data (i.e. measured levels of the substance in plasma and milk at equal time points). If no such data are available, the milk to plasma ratio could, in principle, be calculated on the basis of the pKa, degree of lipid solubility (ie the relative concentrations of ionised and unionised free drug), the degree of protein binding in plasma and milk, and assuming standard pH values for plasma and milk (Rasmussen, 1966).

Calculating the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk

As the elimination rate is equal for all compartments of the body during the terminal phase of elimination, the time needed to eliminate a drug from the body can be estimated by applying the terminal elimination half-life for the substance to the total number of molecules administered. To calculate the total number of molecules administered the following information is required: the total treatment dose given to the animal; the bodyweight of the animal; the molar weight of the drug substance; and Avogadro's number.

The following equation describes the elimination process in the terminal phase:

$$D(t) = D(0) \times e^{-t/t_{el}} \qquad \text{equation 1}$$

in which D is the number of molecules.

The equation can be converted to find the time needed to ensure a total residue burden in the body equivalent to the part of the ADI available to accommodate residues in 1.5 l milk (taking into account the maximum theoretical exposure to residues calculated from the existing tissue MRLs):

$$T = \frac{\ln\left(\left(\frac{dose \times duration}{1000}\right) \times bw \times \frac{A}{M}\right) - \ln(B) \times 1.44 \times t_{1/2}}{24} \qquad \text{equation 2}$$

in which T = time (days), dose = total dose (g/kg bw/day), duration = treatment duration (days), bw = bodyweight (kg), A = Avogadro's number = $6.0 * 10^{23}$, M = Molar mass (g/mol), $t_{1/2}$ = terminal elimination half-life (h), and in which

$$B = \left(\frac{safe\ amount\ in\ \mu g}{M}\right) \times A \times 10^{-6} \qquad \text{equation 3}$$

in which M = Molar mass (g/mol), A = Avogadro's number = $6.0 * 10^{23}$

The output of equation 2 is always rounded to a whole number of days.

Consideration of realistic safe time spans

In making recommendations for safe time spans to be applied between administration of a product and collection of milk for human consumption, consideration will also be given to ensuring compatibility with normal animal husbandry practices.

[3] Ito, S., Lee, A. (2003) Drug excretion into breast milk- overview. Adv Drug Deliv Rev. 55(5): 617-627

Clorsulon

Available data

Study 1. A pharmacokinetic study was provided in which 5 lactating cows were administered a single subcutaneous injection of clorsulon. Plasma and milk levels of clorsulon were recorded.

Study 2. A tissue residue depletion including data on plasma clorsulon levels was provided, in which forty cattle were administered single subcutaneous injections of 2 mg/kg bw clorsulon. Plasma clorsulon levels were monitored for up to 35 days after administration (GLP compliant).

Defining a safe concentration for clorsulon in milk - cattle

No radiolabelled data were available for use in determining an appropriate marker residue for use in milk and on which to base a ratio of marker to total residues. However, as clorsulon was established as the marker residue in cattle tissues (CVMP Summary Report, 2008) and as the parent compound has been identified in bovine milk in a number of studies, clorsulon was also considered to be an appropriate marker residue for use in milk. As the metabolism of clorsulon in milk has not been characterised, any estimation of a marker to total residues ratio should be conservative. It was therefore considered appropriate to apply the marker to total residues ratio of 0.4, established for bovine muscle, to milk as this represented the most conservative marker to total residues ratio established for bovine tissues (marker to total residues ratios in liver and kidney were 0.55 and 0.75, respectively – no marker to total residues ratio was established for fat).

MRLs established muscle, fat, liver and kidney lead to a theoretical maximum daily intake of residues equivalent to 48% of the ADI (CVMP, 2008). The remaining 52% of the ADI corresponds to 62 µg of clorsulon residues. Assuming consumption of 1.5 litre of milk per day and a marker to total residues ratio of 0.4, it is concluded that the concentration of clorsulon in milk that can be considered safe is 16 µg/l.

Residues of clorsulon in milk following subcutaneous administration - cattle

No milk residue data are available following treatment of dairy animals with clorsulon in the dry period. However, based on the results of study 1 reported above, a milk to plasma ratio of 0.3 was derived for the clorsulon. Based on this it was estimated that the safe level in milk (16 µg/l) would occur when the plasma concentration of clorsulon is 53 µg/l. Using this value and the plasma concentrations of clorsulon recorded in study 2 reported above, the time required for depletion of residues to a safe concentration was calculated. The time point at which the 95th percentile of the treated population would have plasma clorsulon concentrations below 53 µg/l with 95% confidence was calculated, using the Time-To-Safe-Concentration (TTSC) method, to be 12 days.

However, veterinary medicinal products containing clorsulon administered subcutaneously authorised in the in the Member States (EU/EEA) are all combination products containing ivermectin as second active substance. Ivermectin does also not have a MRL in milk. Although 12 days was considered sufficient to allow for the depletion of residues of clorsulon to a safe concentration, as ivermectin was not within the scope of this referral and was therefore not evaluated, it was not possible to conclude whether 12 days would also allow residues of ivermectin to deplete to safe levels.

Residues of clorsulon in milk following oral administration - cattle

No data on residues in milk following oral administration were available and no data that would allow extrapolation of residue concentrations from plasma concentrations following oral use were available. Furthermore, the pharmacokinetic data (terminal elimination half-life) required to calculate the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was not available.

However, it is noteworthy that for all substances and routes for which data were made available for this referral, residue levels in milk are always considered to have deplete to a safe level by one year after administration of the substance. A period of one year is therefore considered to represent a conservative default value that can be used where no substance/route specific data are available. While this period of one year is markedly longer than the period of 12 days established for subcutaneously administered clorsulon, it is noteworthy that the only identified oral administration pharmaceutical form containing clorsulon as a single active substance is a bolus, for which the conservative default value is considered appropriate.

It is therefore considered that the only acceptable use of clorsulon in cattle intended for production of milk for human consumption would involve administration to young animals before the first pregnancy and at least 1 year before the first calving.

Closantel

Available data

Study 1. Residue depletion study following a single oral administration of 10 mg/kg bw closantel to 11 pregnant cows 40 to 45 days before expected calving. Milk levels of closantel were measured for up to 84 days post treatment (GCP for animal phase and GLP for analytical phase).

Study 2. Pharmacokinetic study in which 5 heifers and 4 steers were administered a single (oral) dose 10 mg/kg bw ^{14}C-labelled closantel by intubation into the rumen. Plasma radioactivity and closantel levels were monitored for up to 42 days after administration (non GLP).

Study 3. Pharmacokinetic study in which 16 male cattle were administered single subcutaneous injections of one of two closantel formulations, at doses of 5 mg/kg bw. Plasma closantel levels were monitored for up to 1488 hours after administration (GLP study).

Study 4. Pharmacokinetic study in which 4 male and 4 female cattle were administered a single pour-on dose of 20 mg/kg bw closantel. Plasma closantel concentrations were monitored for up to 1848 hours after administration (GLP study).

Study 5. Plasma and milk concentrations of closantel in cattle were reported following a single intramuscular dose.

Study 6. Michiels, M., Meuldermans, W., Heykants, J. (1987) The metabolism and fate of closantel (Flukiver) in sheep and cattle. *Drug Metabolism Reviews*, 18(2&3): 235-251.

Defining a safe concentration for closantel in milk - cattle

No milk residue data are available that would allow empirical determination of a marker residue and a ratio of marker to total residues in milk. However, as closantel was established as the marker residue in cattle tissues (CVMP Summary Report, 1996) and as the substance is known to undergo only limited metabolism *in vivo*, closantel was also considered to be an appropriate marker residue for use in milk. In the absence of data in milk, any estimation of a marker to total residues ratio should be suitably conservative. It was therefore considered appropriate to apply the marker to total residues ratio of 0.7, established for bovine fat, to milk as milk has a high fat content and limited metabolic activity (marker

to total residues ratios established for bovine liver, kidney and muscle are 0.10, 0.80 and 1.00, respectively).

MRLs established in muscle, fat, liver and kidney lead to a theoretical maximum daily intake of residues equivalent to 94.4% of the ADI. The remaining 5.6% of the ADI corresponds to 100 µg of closantel residues. Assuming consumption of 1.5 litre of milk per day and a marker to total residues ratio of 0.7, it is concluded that the concentration of closantel in milk that can be considered safe is 45 µg/l.

Residues of closantel in milk following oral administration - cattle

The oral administration residue depletion study (study 1 above) demonstrated that milk from animals treated during the dry period between 45 and 56 days before calving may contain concentrations of closantel greater than 45 µg/l. This could result in consumer exposure to residues of closantel over the ADI. The data did not show a clear relationship between the length of the dry period and closantel levels in milk from the first milking, and consequently could not be used to determine a time point at which administration could be considered safe for the consumer.

However, closantel depletion profiles have been shown to be similar in milk and plasma, with a milk to plasma ratio of 0.02 (study 5 above). Based on this it was estimated that the safe level in milk (45 µg/l) would occur when the plasma concentration of closantel is 2250 µg/l. Data are available on plasma closantel levels following oral administration (study 2 above) at the recommended dose. Using linear regression to extrapolate from these data suggests that treatment would need to occur 136 days (i.e. 20 weeks) before calving (i.e. during the first half of the gestation period) in order to ensure that closantel levels in milk from the first milking would be below 45 µg/l. This analysis used the 'SCLR' (Safe concentrations based on linear regression) method. It is noted that, in practice, the dry period is generally considerably shorter than 20 weeks.

It is concluded that closantel administered orally should not be used during the dry period. However, the treatment of heifers with closantel administered orally can be regarded as safe as long as it occurs within the first half of the gestation period.

Residues of closantel in milk following subcutaneous administration – cattle

No milk residue data are available following subcutaneous administration of closantel to dairy animals in the dry period. However, data are available on plasma closantel levels following subcutaneous administration (study 3) and, as indicated above, the level of closantel in milk can be considered to be safe when the level in plasma is below 2250 µg/l. Using the Time-To-Safe-Concentration (TTSC) method, the time point at which the 95th percentile of the treated population would have plasma closantel concentrations below 2250 µg/l with 95% confidence was calculated for each of the two formulations for which data were presented in study 3. The time required for plasma closantel levels to deplete to 2250 µg/l was calculated to be 1780 hours (approximately 75 days) for one formulation and 1931 hours (approximately 81 days) for the other formulation. It is noted that, in practice, the dry period is generally considerably shorter than 81 days or 12 weeks.

It is concluded that closantel administered subcutaneously should not be used during the dry period. However, the treatment of heifers with closantel administered subcutaneously can be regarded as safe as long as it occurs only during the first or second trimesters (and not during the third trimester) of the gestation period.

Residues of closantel in milk following pour-on administration – cattle

No milk residue data are available following pour-on administration to dairy animals of closantel in the dry period. However, data are available on plasma closantel levels following pour-on administration

(study 4), and as indicated above, the closantel concentration in milk can be considered safe when the level in plasma is below 2250 µg/l.

Based on the data from study 4, the 'SCLR' (Safe concentrations based on linear regression) method was used to calculate the time point at which the 95th percentile of the treated population would have plasma closantel concentrations below 2250 µg/l with 95% confidence. The time required for closantel levels in plasma to deplete to 2250 µg/l following pour-on application to animals at the same time point was calculated to be 119 days. For the purposes of this referral the time interval of 119 days can be equated to half of the gestation period. It is concluded that consumption of milk from animals treated at the same time point with pour-on closantel during the first half of their pregnancy, would not lead to a total consumer intake exceeding the ADI. However, veterinary medicinal products containing closantel administered as pour-on and authorised in the Member States (EU/EEA) are all combination products containing ivermectin as second active substance. Ivermectin does also not have a MRL in milk. Although 119 days was considered sufficient to allow for the depletion of residues of closantel to a safe concentration, as ivermectin was not within the scope of this referral and was therefore not evaluated, it was not possible to conclude whether 119 days would also allow residues of ivermectin to deplete to safe levels.

Defining a safe concentration for closantel in milk – sheep

No suitable residue data in milk from ewes treated in the dry period are available, no information that would allow the establishment of a ratio of marker to total residues are available and data that would allow the establishment of a milk to plasma ratio in sheep are not available. Furthermore, use of the pharmacokinetic diffusion model based on pKa and protein binding is not possible in this case because information on the level of protein binding is sheep milk is not available (it is known that the binding to sheep milk proteins can deviate significantly from that to cattle milk proteins). In the absence of these data, the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was calculated.

Calculation of the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk requires the terminal half-life for the substance to be known. Half-lives reported for closantel range between 10.8 and 24 days. Using the longest reported figure of 24 days, a molecular weight of 663, a dose of 10 mg/kg bw, and a body weight of 50 kg, the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was calculated to be 299 days. This time period can be rounded up to 1 year.

It is concluded that the only acceptable use of closantel in ewes intended for production of milk for human consumption would involve administration to young animals before the first pregnancy and at least 1 year before the first lambing.

Nitroxinil

Available data

Study 1. Residue depletion study following a single subcutaneous administration of 10 mg/kg bw nitroxinil to 35 pregnant cows. The length of the dry period was monitored, as well as milk levels of nitroxinil for up to 120 days post treatment (non GCP study) – Danaher et al, 2010

Defining a safe concentration for nitroxinil in milk – cattle

No milk residue data are available that would allow empirical determination of a marker residue and a ratio of marker to total residues in milk. However, nitroxinil was established as the marker residue in cattle tissues (CVMP Summary Report, 1998), and is known to be the major residue present in fat, muscle, kidney and plasma. Furthermore, available data suggest that the parent compound is present in milk at comparable or lower levels than in plasma. Nitroxinil was therefore considered to be an

appropriate marker residue for use in milk. In the absence of data in milk, any estimation of a marker to total residues ratio should be suitably conservative. While residues of nitroxinil in milk may be present largely as nitroxinil (as is the case in fat), there have also been reports of nitroxinil conjugates in milk (Whelan et al., 2011). Consequently, it was considered reasonable to use a ratio of marker to total residues of 0.5 for nitroxinil in milk (marker to total residues ratios established for bovine liver, kidney and muscle are 0.04, 0.34 and 1, respectively).

MRLs established in muscle, fat, liver and kidney lead to a theoretical maximum daily intake of residues equivalent to 80% of the ADI. The remaining 20% of the ADI corresponds to 60 µg of nitroxinil residues. Assuming consumption of 1.5 litre of milk per day and a marker to total residues ratio of 0.5, it is concluded that the concentration of nitroxinil in milk that can be considered safe is 20 µg/l.

Residues of nitroxinil in milk following subcutaneous administration to cattle

The only available residue study (study 1) demonstrates that milk from animals whose dry period lasted at least 71 days did not contain nitroxinil at levels above 20 µg/l.

It is concluded that use of nitroxinil-containing products administered by the subcutaneous route should take place before the last trimester of the gestation period in order to ensure that residues in milk would not be at a level that could result in total exposure to residues over the ADI.

Residues of nitroxinil in milk following subcutaneous administration to sheep and goats

No data on residues in milk following subcutaneous administration in these species were available and no data that would allow extrapolation of residue concentrations from plasma concentrations following use in these species were available. Furthermore, the pharmacokinetic data (terminal elimination half-life) required to calculate the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was not available.

However, it is noteworthy that for all substances and routes for which data were made available for this referral, residue levels in milk are always considered to have deplete to a safe level by one year after administration of the substance. A period of one year is therefore considered to represent a conservative default value that can be used where no substance/route specific data are available.

It is therefore considered that the only acceptable use of nitroxinil in sheep and goats intended for production of milk for human consumption would involve administration to young animals before the first pregnancy and at least 1 year before the first lambing/kidding.

Rafoxanide

Available data

Study 1. Biotransformation and excretion study following single oral administration of rafoxanide ^{131}I-rafoxanide to 2 cattle and 2 sheep.

Study 2. Residue depletion study in plasma following single oral administrations of one of two formulations of 7.5 mg/kg bw rafoxanide to 6 cattle and 6 sheep. Plasma levels of rafoxanide were measured for up to 672 hours post treatment (GCP for animal phase and GLP for analytical phase) – Bloomfield, 1991

Defining a safe concentration for rafoxanide in milk – cattle

Based on the data from study 1 the ratio of rafoxanide to total residues in milk of cattle was approximately 0.25 to 0.35. Based on this study, the parent compound, rafoxanide, was concluded to be the appropriate marker residue in milk, and a ratio of marker to total residues of 0.3 was established. Although data were not available that would allow empirical derivation of a marker to total

residues ratio in sheep milk, the ratio of 0.3 was considered to be sufficiently conservative to apply ovine milk as well as to bovine milk.

MRLs established in muscle, fat, liver and kidney lead to a theoretical maximum daily intake of residues equivalent to 75 % of the ADI (CVMP, 2001). The remaining 25% of the ADI corresponds to 30 µg rafoxanide residues. Assuming consumption of 1.5 l of milk per day and a marker to total residues ratio of 0.3, it is concluded that the concentration of rafoxanide in milk that can be considered safe is 6 µg/l.

Residues of rafoxanide in milk following oral administration - cattle

No milk residue data are available following treatment of dairy animals with rafoxanide in the dry period. However, based on the results of study 1 the milk/serum concentration ratio of rafoxanide (measured as radiolabelled Iodine in chloroform extract) was approximately 1/30. Based on this it was estimated that the safe level in milk (6 µg/l) would occur when the plasma concentration of rafoxanide is 0.18 µg/ml.

The 'SCLR' (Safe concentrations based on linear regression)[4] method was used to extrapolate from the combined plasma depletion data available for the two formulations used in study 2. It was concluded that residues in pasma would be below 0.18 µg/l 78 days (11 weeks) after administration.

It is concluded that use of rafoxanide containing products administered orally should take place during the first or second trimesters (and not during the third trimester) of the gestation period in order to ensure that residues in milk would not be at a level that could result in total exposure to residues over the ADI.

Residues of rafoxanide in milk following subcutaneous administration - cattle

No data on residues in milk following subcutaneous administration were available and no data that would allow extrapolation of residue concentrations from plasma concentrations following subcutaneous use. Furthermore, the pharmacokinetic data (terminal elimination half-life) required to calculate the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was not available.

However, it is noteworthy that for all substances and routes for which data were made available for this referral, residue levels in milk are always considered to have deplete to a safe level by one year after administration of the substance. A period of one year is therefore considered to represent a conservative default value that can be used where no substance/route specific data are available.

It is therefore considered that the only acceptable subcutaneous use of rafoxanide in cattle intended for production of milk for human consumption would involve administration to young animals before the first pregnancy and at least 1 year before the first calving.

[4] The SCLR method (CVMP 2000) is intended for use in milk withdrawal period calculations. However, because the type of data are similar the method is also considered appropriate for use here.

Defining a safe concentration for rafoxanide in milk – sheep

No suitable residue data in milk from ewes treated in the dry period are available, and data that would allow the establishment of a milk to plasma ratio in sheep are not available. Furthermore, use of the pharmacokinetic diffusion model based on pKa and protein binding is not possible in this case because information on the level of protein binding is sheep milk is not available. In the absence of these data, the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was calculated.

Calculation of the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk requires the terminal half-life for the substance to be known. Half-lives reported for rafoxanide range between 7 and 16.6 days. Using the longest reported figure of 16.6 days, a molecular weight of 626, a dose of 7.5 mg/kg bw, and a body weight of 50kg, the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was calculated to be 272 days which, for the purposes of this referral, can be rounded up to 1 year.

It is concluded that the only acceptable use of rafoxanide in ewes intended for production of milk for human consumption would involve administration to young animals before the first pregnancy and at least 1 year before the first lambing.

Triclabendazole

Available data

Study 1. Pharmacokinetic study following oral administration of ^{14}C-triclabendazole.

Study 2. Residue depletion study in milk following a single pour-on application of 20 mg/kg bw triclabendazole to 18 pregnant cows 60 days prior to expected calving. Milk concentrations of triclabendazole were measured for up to 20 days after calving (GLP compliant)

Study 3. Residue study in milk following oral administration of triclabendazole to cows around the time of calving. Milk concentrations of triclabendazole and its metabolites were determined over time and the time between treatment and calving was recorded (non GLP study for which limited information on the animal phase of the study is available.

Study 4. Residue study in milk following oral administration of triclabendazole to cows around two months before calving. Milk concentrations of triclabendazole and its metabolites were determined over time and the time between treatment and calving was recorded (non GLP study).

Defining a safe concentration for triclabendazole in milk – cattle

The marker residue established for tissues is the ‘sum of extractable residues which may be oxidised to ketotriclabendazole’. Use of the same marker residue was considered appropriate for milk.

Based on data from study 1 a ratio of marker to total residues of 0.6 for cattle milk was established at 21 days after oral administration of ^{14}C-triclabendazole.

MRLs established in muscle, fat, liver and kidney lead to a theoretical maximum daily intake of residues equivalent to 70% of the ADI (CVMP Summary Report, 2001). The remaining 30% of the ADI corresponds to 27 µg triclabendazole residues. Assuming consumption of 1.5 l of milk per day and a marker to total residues ratio of 0.6, it is concluded that the concentration of triclabendazole in milk that can be considered safe is 10 µg/l.

Residues of triclabendazole in milk following pour-on administration - cattle

The residue depletion study following pour-on administration (study 2) showed that residues were detectable in a small number of animals, sometimes in excess of 10 µg/l. These cases were considered

to have resulted from animals grooming each other. Consequently, it is concluded that residues in milk can only be expected to be below 10 µg/l if animals are prevented from grooming other (treated) animals. However, as it is common practice to keep animals in a group, there is a risk that concentrations of triclabendazole in milk will exceed 10 µg/l, possibly even in untreated (lactating) animals. Consequently, a safe time span for the pour-on use of triclabendazole before calving cannot be established. It is concluded that triclabendazole administered topically as pour-on should not be used in dairy animals.

Residues of triclabendazole in milk following oral administration - cattle

The available data relating to residues in milk following oral administration (study 3) showed a slow but clear depletion of residues in milk in the days after calving. However, residue levels in milk from the first milkings were in the range of 50 to 730 µg/l. Based on these data it was concluded that triclabendazole residues in milk from animals treated 2 to 15 days before calving could be sufficiently high to result in total exposure of residues (in the foodbasket) over the ADI. The data from this residue study in milk were not suitable for determination of a safe pre-calving interval. However, in study 4 longer pre-calving periods were investigated. The results showed that the marker residue in milk at the first milking is below the safe concentration when a pre-calving period of 2 months is respected. It is therefore concluded that use of oral triclabendazole-containing products should take place during the first or second trimesters (and not during the third trimester) of the gestation period.

Defining a safe concentration for triclabendazole in milk - sheep

No suitable residue data in milk from ewes treated in the dry period are available, and data that would allow the establishment of a milk to plasma ratio in sheep are not available. Furthermore, use of the pharmacokinetic diffusion model was not possible as information on the pKa and protein binding for triclabendazole residues that make up the marker residue are not available. In the absence of these data, the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was calculated.

Calculation of the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk requires the terminal half-life for the substance to be known. The longest half-life reported for marker residue was 25 days. Using this value, a molecular weight of 359.66, a dose of 10 mg/kg bw, and a body weight of 50 kg, the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was calculated to be 359 days. For the purposes of this referral this can be equated to 1 year.

It is concluded that the only acceptable use of triclabendazole in ewes intended for production of milk for human consumption would involve administration to young animals before the first pregnancy and at least 1 year before the first lambing.

Residues of triclabendazole in goats' milk

No data on residues in goats' milk were available and no data that would allow extrapolation of residue concentrations from plasma concentrations were available. Furthermore, the pharmacokinetic data (terminal elimination half-life) required to calculate the time needed to ensure a total residue burden equal to a safe number of molecules in 1.5 l milk was not available.

However, it is noteworthy that for all substances and routes of administration for which data were made available for this referral, residue levels in milk are always considered to have deplete to a safe level by one year after administration of the substance. A period of one year is therefore considered to represent a conservative default value that can be used where no substance/route specific data are available.

It is therefore considered that the only acceptable use of triclabendazole in goats intended for production of milk for human consumption would involve administration to young animals before the first pregnancy and at least 1 year before the first lambing.

3. Benefit-Risk Assessment

Flukicides play a critical role in the prevention and control of trematode infections. MRLs in milk have not been established for the flukicidal substances clorsulon, closantel, nitroxinil, rafoxanide and triclabendazole and therefore cannot be used in lactating animals. However, these substances are administered during the dry period for the prevention and treatment of trematode infections in dairy animals. This referral sought to determine whether this use of these substances would result in residues in milk that, when combined with residues of these substances in other food commodities, could result in consumer exposure over the ADI.

The evaluation concludes that use of these substances during the non-lactating period could lead to residue levels in milk that are sufficient to result in consumer exposure over the ADI. The Committee therefore calculated minimum time spans that should elapse between administration of these substances and calving or lambing/kidding for each substance, species and route of administration. In view of the limited data available the Committee considered it appropriate to round these minimum time spans upwards in order to arrive at general recommendations. These are presented in the table below.

Table - Safe time spans between treatment and calving or lambing/kidding for five flukicidal substances

Active substance	Target species	Route of administration	Minimum safe time span	Outcome
Clorsulon	Cattle	subcutaneous	12 days	Not relevant as used in combination products only
Clorsulon	Cattle	Oral[5]	Not possible to determine	Do not use for at least 1 year before the first calving
Closantel	Cattle	Oral	136 days	Do not use during 2nd half of gestation period
Closantel	Cattle	subcutaneous	81 days	Do not use during last trimester of gestation period
Closantel	Cattle	pour-on	119 days	Not relevant as used in combination products only
Closantel	Sheep	subcutaneous	299 days	Do not use for at least 1 year before the first lambing
Closantel	Sheep	oral	299 days	Do not use for at least 1 year before the first lambing
Nitroxinil	Cattle	subcutaneous	70 days	Do not use during last trimester of gestation period
Nitroxinil	Sheep	subcutaneous	Not possible to determine	Do not use for at least 1 year before the first lambing
Nitroxinil	Goats	subcutaneous	Not possible to determine	Do not use for at least 1 year before the first kidding
Rafoxanide	Cattle	Oral	78 days	Do not use during last trimester of gestation period
Rafoxanide	Cattle	subcutaneous	Not possible to determine	Do not use for at least 1 year before the first calving
Rafoxanide	Sheep	oral	272 days	Do not use for at least 1 year before the first lambing
Triclabendazole	Cattle	oral	60 days	Do not use during last trimester of gestation period

[5] Pharmaceutical form for oral administration – bolus

Active substance	Target species	Route of administration	Minimum safe time span	Outcome
Triclabendazole	Cattle	pour-on	No safe time span	Do not use in animals of any age intended to produce milk for human consumption
Triclabendazole	Sheep	oral	359 days	Do not use for at least 1 year before the first lambing
Triclabendazole	Goats	oral	Not possible to determine	Do not use for at least 1 year before the first kidding

It should be noted that many (155) of the clorsulon, closantel, nitroxinil, rafoxanide or triclabendazole containing products are combination products containing other active substances. With regard to these combination products, in 35 of these products a MRL for milk has been established for the second active substance and for 120 no MRL for milk has been established for the second active substance. Although the conclusions shown in the above table are applicable to the flukicidal substance in the product they may not be appropriate for the second active substance. In order to establish the overall appropriateness of the product information with regard to the use in dairy animals the second active substance would need to be considered. As the scope of the current referral was restricted to the evaluation of flukicidal substances only, the depletion of the second active substance was not evaluated and it was not possible to conclude whether the time spans indicated above would also allow residues of the second active substance to deplete to safe levels.

However for combination products administered as pour-on for which the conclusion with regard to the flukicidal substance triclabendazole is that it cannot be used in dairy animals of any age, this conclusion, being the worst case scenario, applies to all pour-on combination products containing triclabendazole (i.e. triclabendazole and moxidectin).

Having considered all the overall package of data submitted the CVMP concluded that the benefit-risk balance for the veterinary medicinal products containing clorsulon, closantel, nitroxinil, rafoxanide or triclabendazole as single active substances (see Annex I) was positive provided that adequate instructions concerning use in dairy animals are included in section 4.11 Withdrawal period(s) of the SPC of the relevant products based on the time spans shown in the above table.

With regard to veterinary medicinal products containing triclabendazole and moxidectin and administered as pour-on to cattle (see Annex I), the Committee concluded that any use in dairy animals might result in unacceptable residue levels in milk. Therefore, the Committee recommended the amendment of section 4.11 Withdrawal period(s) of the SPC of the relevant products to indicate that the products should not be used in dairy animals of any age.

The relevant sections of the package leaflets for all products concerned by this referral should be revised taking into account the recommendetions for section 4.11 Withdrawal period(s) of the SPC.

4. Re-examination procedure

Following the CVMP opinion of 8 March 2012 recomending amendments of section 4.11 Withdrawal period(s) of the SPC for the veterinary medicinal products containing clorsulon, closantel, nitroxinil, rafoxanide or triclabendazole as a single active substance (see Annex I) and for the veterinary medicinal products administered as pour-on to cattle containing triclabendazole and moxidectin (see Annex I), on 23 March 2012, MERIAL notified the Agency of ther intention to request a re-examination of the CVMP opinion. The detailed grounds for re-examination were submitted on 2 May 2012.

The re-examination related to the recommended amendments of section 4.11 Withdrawal period(s) of the SPC for the veterinary medicinal products containing nitroxinil that are administered to cattle.

MERIAL's grounds for requesting a re-examination of the CVMP opinion focused on the fact that the results of a study using its marketed nitroxinil containing solution for injection indicate that by 71 days after administration of the product to dry cattle, residues in milk were at or below 20 µg/l, which the CVMP concluded to be a level of residues in milk that would not represent a consumer safety concern. Based on this, the marketing authorisation holder considered that the CVMP recommendation that nitroxinil containing products should not be used during the last trimester of gestation was unnecessarily conservative for the product in question. The marketing authorisation holder argued further that, in practice, the CVMP recommendation would effectively mean that treatment of dairy animals with nitroxinil would not be an option and that this would, in turn, result in a lack of availability of efficacious treatment for fluke in dairy cattle. The marketing authorisation holder concluded that a period of 71 days between product administration and calving would be sufficient to ensure consumer safety and that such a time span would still allow use of nitroxinil in dry cattle, thus improving treatment options.

CVMP conclusions after the re-examination

It should be noted that the present referral procedure focuses on consumer safety. Issues related to availability of veterinary medicines and animal welfare are outside the scope of this referral.

The CVMP recommendation does not represent a formal withdrawal period. It is a recommendation relating to an approximate, and necessarily conservative, time period that should be allowed to elapse between product administration and calving in order to ensure that nitroxinil residues in milk deplete to safe levels. Indeed, it should be noted that the derivation of a withdrawal period uses established MRLs as the starting point. As the scope of the current referral concerns flukicidal substances for which MRLs have not been established in milk, formal withdrawal periods could be not recommended as part of this evaluation.

A single study using a single product was available relating to the use of nitroxinil in milk producing cattle. A number of deficiencies with the study were noted. In particular, no statistical analysis of the available milk residue depletion study was available with the result that intersubject variability was not taken into account. Other deficiencies in the study, including the fact that it was not GLP compliant and that only the draft study report was provided also reduce the robustness of the study.

In addition, as depletion of nitroxinil residues in milk will be affected by the time between treatment and calving and as, in practice, the calving date is difficult to predict, it is not considered appropriate to express the time period that needs to elapse following product administration in terms of a precise number of days to calving. Finally, the test for residues of nitroxinil in milk, which the marketing authorisation holder suggested could be used to ensure that residue levels remain below the safe level even following early calvings, has not been taken into account in this evaluation due to the lack of detailed information on the test in question.

Based on the considerations above the Committee concluded that a conservative recommendation would be appropriate. The statement 'do not use during the last trimester of pregnancy' was considered appropriate to overcome uncertainties resulting from the identified deficiencies.

It is also noteworthy that the CVMP recommendation relating to the use of nitroxinil in cattle is meant to be applicable to all nitroxinil containing products including those with different formulations and strengths. While no evidence was available to indicate that the pharmacokinetic and residue depletion behaviour following administration of the different nitroxinil containing products would be identical to that seen in the available study, the conservative approach adopted in the interpretation of the available data ensures that the resulting recommendation is valid for all nitroxinil containing products.

After reviewing the documentation submitted by the marketing authorisation holder and after considering the information provided during the oral explanation, the CVMP concluded that there were

not sufficient scientific grounds to revise its conclusions of 8 March 2012 on the restrictions that should be applied to the use of nitroxinil in dairy cattle in order to avoid residues in milk occurring at levels that could compromise consumer safety.

It should be noted that while the recommended time spans reflect safe exposure levels for the consumer, residues (at safe levels) may still be found in milk upon control.

It should also be noted that since the commencement of this referral, MRLs have been recomended for clorsulon in bovine milk, for closantel and nitroxinil in bovine and ovine milk, and for triclabendazole in milk of all ruminants. The conclusions of this referral will remain appropriate even if the recommended milk MRLs are established for the above substances, unless product specific data are submitted to the national competent authorities for the establishment of milk withdrawal periods.

Grounds for amendment of the summaries of product characteristics and package leaflets

Whereas:

- The scope of the referral was to determine whether measures are necessary to ensure that the use during the non-lactating period, of veterinary medicinal products containing flukicidal substances for which maximum residue limits have not been established in milk would not lead to residues in milk that, combined with residues of these flukicidal substances from other foodstuffs, would result in consumer exposure exceeding the exceeding the acceptable daily intake;
- on the basis of the data provided it was considered that the risk associated with the absence of established MRLs in milk for clorsulon, closantel, nitroxinil, rafoxanide or triclabendazole may present a risk to public health;
- the CVMP considered that the overall benefit-risk balance is positive for the products containing clorsulon, closantel, nitroxinil, rafoxanide or triclabendazole as single active substances, and for the veterinary medicinal products administered as pour-on containing triclabendazole and moxidectin, subject to inclusion of adequate instructions and warning sentences concerning the use in dairy cattle in the product information;

the CVMP has recommended variations of the marketing authorisations for the veterinary medicinal products containing clorsulon, closantel, nitroxinil, rafoxanide or triclabendazole as single active substances, and for the triclabendazole-containing veterinary medicinal products administered as pour-on (see Annex I) in order to amend the Summaries of Product Characteristics and package leaflets in line with recommended changes in the product information as set out in Annex III.

As the scope of the current referral was restricted to the evaluation of flukicidal substances, the second active substances in combination products were not assessed. Therefore no conclusion could be drawn on the instructions to be included in the product information of combination products, with the exception of veterinary medicinal products in Annex I containing triclabendazole and moxidectin and administered as pour-on, for which the conclusion on the flukicidal substance is that it cannot be used in dairy animals at any time. For all combination products other than those that cannot be used in dairy animals at any time, the national competent authorities will need to determine whether the recommendations concerning the substances evaluated in this referral are sufficient to ensure that residues in milk of the non-flukicidal active substance will not occur at unsafe levels.

Annex III

Amendments in the relevant sections of the summary of product characteristics and package leaflet

Amendments in the relevant sections of the summary of product characteristics

A. <u>For products listed in Annex I containing clorsulon as sole active substance and administered orally to cattle:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first calving in heifers intended to produce milk for human consumption.

B. <u>For products listed in Annex I containing closantel as sole active substance and administered orally to cattle:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the second half of pregnancy in heifers which are intended to produce milk for human consumption.

C. <u>For products listed in Annex I containing closantel as sole active substance and administered subcutaneously to cattle:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

D. <u>For products listed in Annex I containing closantel as sole active substance and administered subcutaneously or orally to sheep:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

E. <u>For products listed in Annex I containing nitroxinil as sole active substance and administered subcutaneously to cattle:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

F. <u>For products listed in Annex I containing nitroxinil as sole active substance and administered subcutaneously to sheep and goats:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in animals producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing/kidding in animals intended to produce milk for human consumption.

G. <u>For products listed in Annex I containing rafoxanide as sole active substance and administered orally to cattle:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

H. <u>For products listed in Annex I containing rafoxanide as sole active substance and administered subcutaneously to cattle:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first calving in heifers intended to produce milk for human consumption.

I. <u>For products listed in Annex I containing rafoxanide as sole active substance and administered orally to sheep:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

J. <u>For products listed in Annex I containing triclabendazole as sole active and administered orally to cattle:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

K. <u>For products listed in Annex I containing triclabendazole as sole active and administered orally to sheep:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

L. <u>For products listed in Annex I containing triclabendazole as sole active and administered as orally to goats:</u>

4.11 Withdrawal period(s)

……..

Not authorised for use in goats producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first kidding in goats intended to produce milk for human consumption.

M. <u>For products listed in Annex I containing triclabendazole and moxidectin as active substances and administered as pour-on to cattle:</u>

4.11 Withdrawal period(s)

……..

Do not use in cattle of any age intended to produce milk for human consumption.

Amendments in the relevant sections of the package leaflet:

A. <u>For products listed in Annex I containing clorsulon as sole active substance and administered orally to cattle:</u>

10. WITHDRAWAL PERIOD

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first calving in heifers intended to produce milk for human consumption.

B. <u>For products listed in Annex I containing closantel as sole active substance and administered orally to cattle:</u>

10. WITHDRAWAL PERIOD

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the second half of pregnancy in heifers which are intended to produce milk for human consumption.

C. <u>For products listed in Annex I containing closantel as sole active substance and administered subcutaneously to cattle:</u>

10. WITHDRAWAL PERIOD

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

D. <u>For products listed in Annex I containing closantel as sole active substance and administered subcutaneously or orally to sheep:</u>

10. WITHDRAWAL PERIOD

……..

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

E. <u>For products listed in Annex I containing nitroxinil as sole active substance and administered subcutaneously to cattle:</u>

10. WITHDRAWAL PERIOD

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

F. <u>For products listed in Annex I containing nitroxinil as sole active substance and administered subcutaneously to sheep and goats:</u>

10. WITHDRAWAL PERIOD

……..

Not authorised for use in animals producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing/kidding in animals intended to produce milk for human consumption.

G. For products listed in Annex I containing rafoxanide as sole active substance and administered orally to cattle:

10. WITHDRAWAL PERIOD

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

H. For products listed in Annex I containing rafoxanide as sole active substance and administered subcutaneously to cattle:

10. WITHDRAWAL PERIOD

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first calving in heifers intended to produce milk for human consumption.

I. For products listed in Annex I containing rafoxanide as sole active substance and administered orally to sheep:

10. WITHDRAWAL PERIOD

……..

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

J. For products listed in Annex I containing triclabendazole as sole active and administered orally to cattle:

10. WITHDRAWAL PERIOD

……..

Not authorised for use in cattle producing milk for human consumption including during the dry period. Do not use during the last trimester of pregnancy in heifers which are intended to produce milk for human consumption.

K. For products listed in Annex I containing triclabendazole as sole active and administered orally to sheep:

10. WITHDRAWAL PERIOD

……..

Not authorised for use in ewes producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first lambing in ewes intended to produce milk for human consumption.

L. For products listed in Annex I containing triclabendazole as sole active and administered as orally to goats:

10. WITHDRAWAL PERIOD

……..

Not authorised for use in goats producing milk for human consumption including during the dry period. Do not use within 1 year prior to the first kidding in goats intended to produce milk for human consumption.

M. <u>For products listed in Annex I containing triclabendazole and moxidectin as active substances and administered as pour-on to cattle:</u>

10. WITHDRAWAL PERIOD

……..

Do not use in cattle of any age intended to produce milk for human consumption.